REMARKS

Claims 1, 2, 4, 6, 8-12, 50, 51, 53-55, 57, 58, and 61-114 were pending in this application. Claims 1, 2, 4, 6, 50, 51, 53, 55, 57, 58, 84, 87, 88- 95, 98, 100, 101, 102, and 107 have been amended and claims 76, 77, 85, 86, 113 and 114 have been cancelled. In addition, the Examiner has indicated that claims 87-114 drawn to murine T-bet nucleic acid molecules, host cells, and vectors will not be rejoined based on the new grounds of rejection of linking claim 51. Accordingly, the Examiner has withdrawn claims 87-114 as being drawn to a non-elected invention. Accordingly, upon entry of this amendment, claims 1, 2, 4, 6, 8-12, 50, 51, 53-55, 57, 58, and 61-75, and 78-84 will be pending.

No new matter has been added. Any amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was performed solely in the interest of expediting prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Claims 4, 6, and 53 are free of the art.

Sequence Disclosure

The Examiner acknowledges submission of the corrected CRF and Sequence Listing filed January 26, 2006 with Applicants' response, however states that the application still fails to comply with the requirements of 37 C.F.R. §1.821 through C.F.R. §1.825, because the "specification fails to disclose SEQ ID NOs. for the nucleotide sequences on pg. 14 and pg. 72, paragraph 3.".

Applicants respectfully submit the amendments to the specification presented herein render the Examiner's rejection moot. Accordingly, Applicants request reconsideration and withdrawal of the rejection under C.F.R. §1.821- C.F.R. §1.825.

Withdrawal of Certain Objections/Rejections

Applicants gratefully acknowledge the Examiner's indication that the following objections/rejections have been withdrawn:

the rejection of claims 50 and 64 under 35 U.S.C. §112, second paragraph, as being indefinite for the recitation of the term "initiation of Th1 cell differentiation of Thp cells and Th2 cells";

the rejection of claim 64 under 35 U.S.C. §112, second paragraph, as being indefinite and lacking antecedent basis in for the recitation of "IL-2"; and

the rejection of claims 1, 2, 4, 6, 8-12, 50, 51, 53-55, and 57-59 under the judicially created doctrine of obviousness-type double patenting.

Rejection of Claims 50, 58, and 64 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 50 and 64 under 35 U.S.C. §112, second paragraph, as being indefinite for the recitation of "differentiating Thp cells and Th2 cells into Thl cells", because, according to the Examiner, "[w]hile a polypeptide may be able to induce differentiation, it cannot 'differentiate' cells as claimed."

Without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have amended claim 50, from which claim 64 depends, to recite "***inducing the differentiation of Thp cells and Th2 cells into Th1 cells***". Accordingly, Applicants request reconsideration and withdrawal of this §112, second paragraph rejection of claims 50 and 64.

The Examiner has rejected claim 58 under 35 U.S.C. §112, second paragraph, as being indefinite for the recitation of "comprising at least 700 nucleotides which is complementary to SEQ ID NO:1", because, according to the Examiner, "[i]t is not clear whether the claims encompass nucleic acids of at least 700 nucleotides which are complementary over any length to SEQ ID N0:l, or whether the claims are limited to nucleic acids which have 700 nucleotides complementary to SEQ ID NO: 1."

Without acquiescing to the Examiner's rejection and solely in the interest of expediting examination, Applicants have amended claim 58 to recite "***comprising at least 700 nucleotides which are complementary to at least 700 nucleotides of SEQ ID NO:1***". Accordingly,

Applicants request reconsideration and withdrawal of this §112, second paragraph rejection of claim 58.

Rejection of Claims 54, 57, 76, 77, 85, and 86 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 54, 76, and 77 under 35 U.S.C. §112, first paragraph, "as failing to comply with the written description requirement." "This is a new matter rejection." In particular, the Examiner is of the opinion that "the specification discloses recombinant T-bet protein can be prepared as an extracellular protein by operatively linking a heterologous signal sequence to the protein. This disclosure is insufficient to provide support for claims drawn to a nucleic acid further comprising a nucleotide sequence encoding any heterologous polypeptide."

Applicants respectfully traverse the foregoing rejection for the following reasons. Applicants submit that there is sufficient written description in Applicants' specification regarding fusion proteins such that one of ordinary skill in the art would have understood that Applicants were in possession of the claimed invention at the time the application was filed. More specifically, Applicants' specification teaches at page 19, lines 19-25 that

> another aspect of the invention pertains to ***isolated nucleic acid molecules encoding T-bet fusion proteins***. Such nucleic acid molecules, comprising at least a first nucleotide sequence encoding a T-bet protein, polypeptide or peptide operatively linked to a second nucleotide sequence encoding a non-T-bet protein, polypeptide or peptide, can be prepared by standard recombinant DNA techniques.

The specification further provides examples of some specific fusion proteins. For example, as indicated by the Examiner, Applicants specification teaches at page 24, lines 1-14

> recombinant T-bet protein can be prepared as a extracellular protein by operatively linking a heterologous signal sequence to the amino-terminus of the protein such that the protein is secreted from the host cells.

Moreover, Applicants specification also teaches that an isolated nucleic acid molecule encoding a T-bet polypeptide can be linked to such non-T-bet polypeptides as GST, HA (see, *e.g.*, page 30, line 27, through page 31, lines 1-4, the specification), GAL4 (see, *e.g.*, page 42,

lines 24-31 of the specification), and the repressor domain of the *Drosophila* engrailed protein (see, *e.g.*, page 71, lines 21-31). Applicants' specification also provide working examples of T-bet fusion proteins. For example, Example 7 at page 68, lines 32-34 teaches the construction of a fusion protein comprising a T-bet polypeptide and GFP, and Example 12, page 71, lines 21-32 teaches the construction of a fusion protein comprising a T-bet polypeptide and the repressor domain of the *Drosophila* engrailed protein.

Based on the foregoing, Applicants submit that the recitation of a "nucleic acid molecule further comprising a nucleotide sequence encoding a heterologous polypeptide" is supported by the instant specification and thus does not constitute new matter.

The Examiner has also rejected claims 57, 85, and 86 under 35 U.S.C. §112, first paragraph, "as failing to comply with the written description requirement." "This is a new matter rejection." In particular, the Examiner is of the opinion that

> the specification discloses labeled nucleic acid probes that hybridize to T-bet mRNA, including probes such as the T-bet DNA of SEQ ID NO: 1 or 3. This specific example of labeled probes comprising SEQ ID NO: 1 or 3 is insufficient to provide adequate support for new claims drawn to a detectably labeled nucleic acid which encodes SEQ ID NO: 2 or a polypeptide 95% identical to SEQ ID NO: 2, or a detectably labeled nucleic acid which has at least 90% identity with SEQ ID NO: 1.

Without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have canceled claims 85 and 86 and amended claim 57 to depend from claim 51 such that an isolated nucleic acid molecule which hybridizes to the complement of SEQ ID NO:1 under stringent conditions is labeled with a detectable substance. As indicated by the Examiner, "the specification discloses labeled nucleic acid probes that hybridize to T-bet mRNA, including probes such as the T-bet DNA of SEQ ID NO: 1 or 3" Accordingly, Applicants request reconsideration and withdrawal of this §112, second paragraph rejection of claims 57.

Rejection of Claims 1, 2, 4, 6, 8-12, 50-51, 53-58, and 61-86
Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1, 2, 4, 6, 8-12, 50-51, 53-58, and 61-86 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." More specifically, the Examiner is of the opinion that

> [t]here is insufficient written description to demonstrate that applicant was in possession of the claimed genus of nucleic acids that are "complements thereof" or "complementary to" SEQ ID NO: 1 or the nucleotide sequence encoding SEQ ID NO: 2, "90% identical with SEQ ID NO:1", "encodes a polypeptide 95% identical to SEQ ID NO: 2", or "a fragment of at lest 700 contiguous nucleotides of SEQ ID NO: 1."

Applicants respectfully traverse the foregoing rejection and submit that there is sufficient written description in Applicants' specification regarding the claimed genus of nucleic acids that are "complements thereof" or "complementary to" SEQ ID NO: 1 or the nucleotide sequence encoding SEQ ID NO: 2, "90% identical with SEQ ID NO:1", "encodes a polypeptide 95% identical to SEQ ID NO: 2", or "a fragment of at lest 700 contiguous nucleotides of SEQ ID NO: 1 to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by 35 U.S.C. §112, first paragraph (see M.P.E.P. 2163.02).

Amended claim 1, and claims dependent therefrom, are directed to isolated nucleic acid molecules comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO:2, or ***which is complementary thereto over its full length***. Amended claim 2 is directed to the nucleic acid molecule of claim 1, which comprises the nucleotide sequence shown in SEQ ID NO:1, or ***which is complementary thereto over its full length***. Claim 4 is directed to isolated nucleic acid molecules, which have at least 90% nucleotide identity with at least ***700 contiguous nucleotides of SEQ ID NO:1, and which encodes a polypeptide that binds a consensus T-box site in DNA and modulates IFN-γ production***. Claim 6 is directed to isolated nucleic acid molecules, which have at least 90% nucleotide identity with SEQ ID NO:1 ***over its full length, and which encodes a polypeptide that binds a consensus T-box site in DNA and modulates IFN-γ production***. Claim 51 is directed to isolated nucleic acid molecules which hybridize to the complement of the nucleic acid molecule set forth in SEQ ID NO:1 ***over the full length of the isolated nucleic acid***

molecule in 6X SSC at 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C under stringent conditions, wherein said nucleic acid molecule encodes a polypeptide that ***binds a consensus T-box site in DNA and modulates IFN-γ production.*** Claim 53 is directed to isolated nucleic acid molecules which encode ***a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2, wherein said nucleic acid molecule encodes a polypeptide that binds to a consensus T-box site in DN and modulates IFN-γ production***. Amended claim 55 is directed to isolated nucleic acid molecules ***consisting of at least 700 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, or a nucleotide sequence complementary thereto, over the full length of the isolated nucleic acid molecule***. Amended claim 58 is directed to isolated nucleic acid molecules ***consisting of at least 700 nucleotides which are complementary to at least 700 nucleotides of SEQ ID NO:1***.

The Examiner is of the opinion that

> [t]he instant specification does not define the terms "complement thereof" or "complement of" as recited in Claims 1-2, 51, and 55. Therefore, "complements" might encompass a sequence of any length. For example, 10 nucleotide fragments "complementary" to SEQ ID NO: 1 might be encompassed by the claims. Likewise, Claim 58 recites a nucleic acid molecule comprising at least 700 nucleotides which is "complementary" to SEQ ID NO: 1. However, the claims do not specifically identify which portion is "complementary", and thus the claims encompass nucleic acid molecules of 700 nucleotides that contain any portion complementary to SEQ ID NO: 1 (*i.e.* even only 10 nucleotides). Furthermore, the nucleic acid molecules of claims 1, 2, 55, and 58 need not even encode a protein of similar function to the T-bet. Thus, the genus of nucleic acid molecules encompassed by "complements thereof" or "complementary to" is virtually unlimited, and might encompass structurally and functionally distinct nucleic acids. Additionally, Applicant has not disclosed any species that are the "complement of" or "complementary to" SEQ ID NO: 1.

With respect to the Examiner's assertion that the term "complement" is not defined in the specification, Applicants submit that the term "complement" is a term of art and would be well known and readily understood by one of skill in the art. Applicants submit that given any nucleotide sequence, a skilled artisan can readily determine the complement of that nucleic acid sequence by determining the nucleotide that would hybridize to each nucleotide of a given sequence (*e.g.*, A:T, C:G). Moreover, although the passage is directed to antisense nucleic acid

molecules, Applicants' specification teaches at page 10, lines 2-6 that the complement of a sense nucleic acid molecule can hydrogen bond to an antisense nucleic acid molecule, *i.e.,* is complementary, and at page 18, lines 26-28, Applicants specification teaches

> [g]iven the coding strand sequences encoding T-bet disclosed herein (*e.g.*, SEQ ID NOs: 1 and 3, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing.

With respect to the Examiner's assertions that the "nucleic acid molecules encompassed by "complements thereof" or "complementary to" is virtually unlimited", Applicants submit that, as amended, the claimed nucleic acid molecules are structurally and functionally related, *i.e.,* complementary over at least 700 nucleotides or over the full length of SEQ ID NO:1, bind to a consensus T-box site in DNA and modulate IFN-γ production. Thus, based on the extensive knowledge available in the art in the art at the time of the invention, the ample guidance provided in the specification and the references cited therein, a person of ordinary skill in the art would understand that Applicants were in possession of the claimed complementary nucleic acid molecules.

The Examiner is further of the opinion that:

> nucleic acids that are "90% identical with SEQ ID NO:1" or "encode a polypeptide 95% identical to SEQ ID NO: 2" is the recitation of a broad genus of nucleic acid molecules. For example, SEQ ID NO: 1 is -1600 nucleotides in length. Therefore, nucleic acids "90% identical" with SEQ ID NO: 1 might be approximately 160 nucleotides (*i.e.* about 10%) different than SEQ ID NO: 1. Thus, the claims encompass a virtually unlimited number of nucleic acids with mutations, deletions or additions up to -160 nucleotides in length. Furthermore, the only claimed functional limitation for said nucleic acids is binding to a consensus T-box site. Therefore, the claims encompass nucleic acids that encode proteins that only bind to a T-box site, but might not mediate any other T-bet function (for example the ability to induce IFN- γ production). Thus, these nucleic acids might differ functionally in that some might encode a protein that induces IFN-γ, while some might only be able to bind a T-box site. Furthermore, the claims also encompass fragments of SEQ ID NO: 1 "of at least 700 contiguous nucleotides in length". Since SEQ ID NO: 1 is -1600 nucleotides, the genus encompassed by said fragments is extremely large. In addition, there is no limitation that the fragments of claim 55 even function to encode a functional T-bet protein. Furthermore, Applicant has not disclosed any species of nucleic acids "90% identical", 95% identical" or any specific nucleic acid fragments. Thus, one of skill

> in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus See Eli Lilly, 119 F. 3d 1559, 43, USPQ2d 1398.

As the Examiner is aware, the Federal Circuit has addressed the sufficiency of a disclosure in meeting the written description requirement of 35 U.S.C. §112 for claims to a genus of cDNAs. Specifically, the Federal Circuit stated that

> [a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus ***or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus*** [*emphasis added*].

The Regents of the University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Accordingly, it is well settled that a claim to a genus of compounds satisfies the written description requirement if the specification either defines a representative number of its members falling within the scope of the genus by disclosing the sequence or if the specification defines the structural features common to a substantial portion of the genus. It is Applicant's position that the instant specification meets the written description requirements articulated by the Federal Circuit in Eli Lilly.

In particular, Applicants would like to bring to the Examiner's attention Example 14 of the *Revised Interim Written Description Guidelines Training Materials*. This Example provides that a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rational behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity." The Guidelines also provide that "[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making

variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art."

Similarly, in the present case, claims 4, 6, 53, and claims dependent therefrom, are directed to nucleic acid molecules that are 90-95% identical to SEQ ID NO:1 (claims 6 and 53) or to nucleic acid molecules which have at least 90% nucleotide identity with at least 700 contiguous nucleotides of SEQ ID NO:1, wherein said nucleic acid molecules encode a polypeptide that binds a consensus T-box site in DNA and modulate IFN-γ production. Applicants have disclosed in the instant specification methods for identifying nucleic acid molecules with at least 90-95% identity of SEQ ID NO:1 (see, *e.g.*, page 8, line 37, through page 9, lines 1-35 of the specification, Example 2 at page 63 of the specification, and Figure 1) as well as exemplary consensus T-box binding sites (see, *e.g.*, page 14, lines 20-23 of the specification, and assays to determine whether a nucleic acid molecule encodes a polypeptide that binds to a consensus T-box site in DNA (see, for example, Example 3 at page 64 of the specification). Thus, based on the teachings in Applicants' specification, one of skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing.

In view of the foregoing, Applicants respectfully submit that the instant specification satisfies the requirements of 35 U.S.C. §112, first paragraph for written description and, accordingly, respectfully request that the Examiner reconsider and withdraw of this rejection.

Rejection of Claims 1, 2, 8, 10, 51, 55, 58, 67, and 69 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 2, 8, 10, 51, 55, 58, 67, and 69 under 35 U.S.C. § 102(b) as being anticipated by Bulfone, *et al.* (1995) *Neuron* 15:63-78. Specifically, the Examiner is of the opinion that

> Bulfone teaches an isolated nucleic acid that encodes Tbr-1, which is a T-box transcription factor (i.e. binds a T-box site in DNA - see abstract and pg. 64-65 in particular). Furthermore, the nucleic acid taught by Bulfone is complementary to SEQ ID NO: 1 of the instant application over certain portions of the sequence. Thus, Tbr-1 nucleic acid comprises a "complement" of SEQ ID NO: 1 (see for example residues 691-707 of Tbr-1, which are complementary to residues 465-481 of SEQ ID NO: 1). Claim 51 is included since "a complement of SEQ ID NO: 1" might comprise any portion of SEQ ID NO: 1 (for example residues 465-481), and thus Tbr-1 would hybridize to "a complement" of SEQ ID NO:1.

> Claim 58 is included since Tbr-1 is at least 700 nucleotides and "is complementary" over certain portions of the sequence to SEQ ID NO: 1. Additionally, Bulfone teaches clones (*i.e.* vectors and host cells) comprising Tbr-1 nucleic acid (see pg. 76 in particular).

Applicants respectfully traverse the foregoing rejection under 35 U.S.C. §102 and request reconsideration. As the Examiner is well aware, for a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir.1987). Claim 1 (from which claims 2, 8, and 10 depend), as amended, is directed to ***an isolated nucleic acid molecule comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO:2, or which is complementary thereto over its full length***. Claim 4 (from which claim 69 depends), as amended, is directed to ***an isolated nucleic acid molecule, which has at least 90% nucleotide identity with at least 700 contiguous nucleotides of SEQ ID NO:1, and which encodes a polypeptide that binds a consensus T-box site in DNA and modulates IFN-γ production***. Claim 51, as amended, is directed to isolated nucleic acid molecules which hybridize to the complement of the nucleic acid molecule set forth in SEQ ID NO:1 ***over the full length of the isolated nucleic acid molecule*** in 6X SSC at 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C under stringent conditions, wherein said nucleic acid molecule encodes a polypeptide that ***binds a consensus T-box site in DNA and modulates IFN-γ production.*** Amended claim 55 (from which claim 67 depends) is directed to isolated nucleic acid molecules ***consisting of at least 700 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, or a nucleotide sequence complementary thereto, over the full length of the isolated nucleic acid molecule***. Amended claim 58 is directed to isolated nucleic acid molecules ***consisting of at least 700 nucleotides which are complementary to at least 700 nucleotides of SEQ ID NO:1***.

Bulfone, *et al.* teach the identification and initial characterization of T-Brain-1, a transcription factor related to *Brachyury*, which is strongly expressed in postmitotic cells of the forebrain, skin, and epithelium of the tongue. Bulfone, *et al.* teach that T-Brain-1 is a member of the T-box family of proteins (see page 64, right-hand column, third full paragraph), as is T-bet (see, page 8, lines 2-6 of the specification). However, Bulfone, *et al.* do not teach or suggest ***an isolated nucleic acid molecule comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO:2, or which is complementary thereto over its full length, an isolated nucleic acid***

molecule, which has at least 90% nucleotide identity with at least 700 contiguous nucleotides of SEQ ID NO:1, and which encodes a polypeptide that binds a consensus T-box site in DNA and modulates IFN-γ production, an isolated nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule set forth in SEQ ID NO:1 over the full length of the isolated nucleic acid molecule in 6X SSC at 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C under stringent conditions, wherein said nucleic acid molecule encodes ***a polypeptide that binds a consensus T-box site in DNA and modulates IFN-γ production, an isolated nucleic acid molecule consisting of a fragment of at least 700 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, or a nucleotide sequence complementary thereto over the full length of the isolated nucleic acid molecule,*** or ***an isolated nucleic acid molecule comprising at least 700 contiguous nucleotides which is complementary to at least 700 nucleotides of SEQ ID NO:1.*** Thus, Bulfone, *et al.* fail to teach or suggest each and every limitation of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 8, 10, 51, 55, 58, 67, and 69 under 35 U.S.C. §102(b).

SUMMARY

It is respectfully submitted that the amendments and comments presented herein place the application in condition for allowance.

Should the Examiner feel that a telephone conference with Applicant's Attorney would expedite prosecution of the application and allowance of the claims, the Examiner is urged to contact the undersigned representative at (617) 227-7400.

Applicants submit herewith the requisite fee associated with the filing of this Amendment. However, should any additional fee be due, please charge such fee to our Deposit Account No. 12-0080, under Order No. HUI-040CP, from which the undersigned is authorized to draw.

Dated: June 30, 2006

Respectfully submitted,

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